Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

Date: June 22, 2000

To: Joseph Bekisz, BLA Committee Chair, HFM-550

From: Deborah Trout, BLA Committee Member, HFM-675

Through: Julia Lukas, Branch Chief, HFM-675

Subject: Review of Biologics License Application (BLA) from Schering-Plough Co., (Brinny) for the manufacture of Peginterferon alfa-2b ; STN Number 103949/0

My review includes an evaluation of the following sections submitted in Schering's BLA application (reference is made to the table of Contents in Volume 1.2 of their submission, STN number 103949/0: Volumes 1.2 (tabs 4.A.1, 4.A.2, 4.A.3, 4.A.3.1-4, 4.A.4, 4. and A.4.1-2), 1.3 (tabs 4.A.7, 4.B.1, 4.B.2, 4.B.3, 4.B.4.1, 4.B.4.2, 4.B.5.1, and 4.B.5.2), 1.4 (tab 4.B.6, 4B.7), and 1.5 (tab 4.D). This review memorandum is comprised of two sections. The first section is issues that can be addressed in the pre-license inspection and the second section is my review narrative

Section I: Pre-license Inspection Issues

1. A "guideline" acceptance limit of [redacted] is applied to the [redacted] analysis of peginterferon alfa-2b Drug Substance. In the event that the guideline level is exceeded, an investigation is conducted to assess the acceptability of the Drug Substance for further processing. The submission indicates that an option exist to [redacted] is exceeded. Please [redacted] procedures during the pre-license inspection. Verify that the firm has written procedures describing a system for [redacted] that do not conform to specification and to assure that any [redacted] will conform to release specifications.

2. Please review assay validation for both the [redacted] release testing during the pre-license inspection.

3. There are [redacted] Purification Areas located within the [redacted]. Peginterferon Alfa-2b Drug Substance is produced in [redacted] The following is a list of

products purified in [redacted] Interferon Alfa – 2b (IFN) (Commercial) and [redacted] (Clinical). Please review changeover and cleaning procedures for [redacted] during the pre-license inspection. In addition, please obtain a list of dedicated and non-dedicate production equipment used in the Peginterferon Alfa-2b Drug Substance manufacturing process.

4. All processing rooms within [redacted] have a room air classification of [redacted] The submission indicates that all critical open operations are performed under either laminar airflow canopies or laminar airflow hoods. Please review HVAC validation, and routine monitoring data to determine if the class [redacted] area is adequately controlled for purification operations. The monitroing program should include non-viables as well as surface and airborne viables. In addition, please determine if final formulation is conducted in a class [redacted] area with at least [redacted] viable and nonviable particulate monitoring during dynamic conditions since there are no other purification steps to reduce [redacted] by product levels.

5. Please review the process validation for the [redacted] The firm should have data demonstrating the performance of the [redacted] over the proposed lifetime of the [redacted] In addition, please review process validation data for the [redacted] feed hold time of [redacted] at [redacted] with an associated [redacted] limit.

6. Please review sanitization effectiveness validation for the [redacted] units used to concentrate and [redacted] the Peginterferon Alfa-2b Drug Substance.

7. Batch [redacted] had an [redacted] result of [redacted] (specification is [redacted]. Please review the investigation initiated in response to exceeded limit.

8. Please review qualification of the container closure system. Qualification may include characterization for solvent and gas permeation, light transmittance, closure integrity, ruggedness in shipment, protection against microbial contamination through the closure, and compatibility and safety of the packaging components as appropriate.

9. The Batch Product Record (BPR) states that the [redacted] vials filled are designated as the "after filtration sterility" test samples. Please verify that the product is filtered into a [redacted] and determine if the filtration is completed [redacted] If not, what volume of product is filtered prior to [redacted]

10. Please review filter validation studies [redacted] for the [redacted] filter used to sterilize the Drug Product.

11. Throughout the drug substance manufacture, there are several filtration operations. Because there is an associated [redacted] limit following filtration [redacted] is not necessary, however the firm should have filter compatibility and extractable information available for review.

12. The submission indicates that WFI use points are tested periodically to assure that the water continuously meets USP quality. Please review [redacted] data for six months of water monitoring for points of use servicing [redacted]

13. Please review the stability testing program for PEG-Intron Drug Substance and Drug Product. A documented, ongoing, testing program should be in place to assess the stability characteristics, and the results should be used to confirm appropriate storage conditions and retest dates.

14. Please review the following regarding equipment cleaning during the inspection: The frequency of routine or periodic testing following the cleaning procedure, sampling procedure, residual [redacted] detection, and frequency of revalidation. If the cleaning procedure is manual, the firm should have validation demonstrating reproducibility and routine testing to ensure validated process is maintained. In addition, residual limits and acceptance criteria should be achievable and verifiable. The manufacture should be able to document by means of data that the level of residuals and acceptance criteria are scientifically sound.

15. Review and verify that a complete validation has been performed and that routine monitoring is being conducted on the [redacted] system in [redacted]

16. Please clarify if all raw materials are tested for identity. It is required that for critical raw materials, the COA should be supplemented by verification of the vendor's critical assay results using a validated in-house assay or those of a qualified contract laboratory.

Section II: Review Narrative

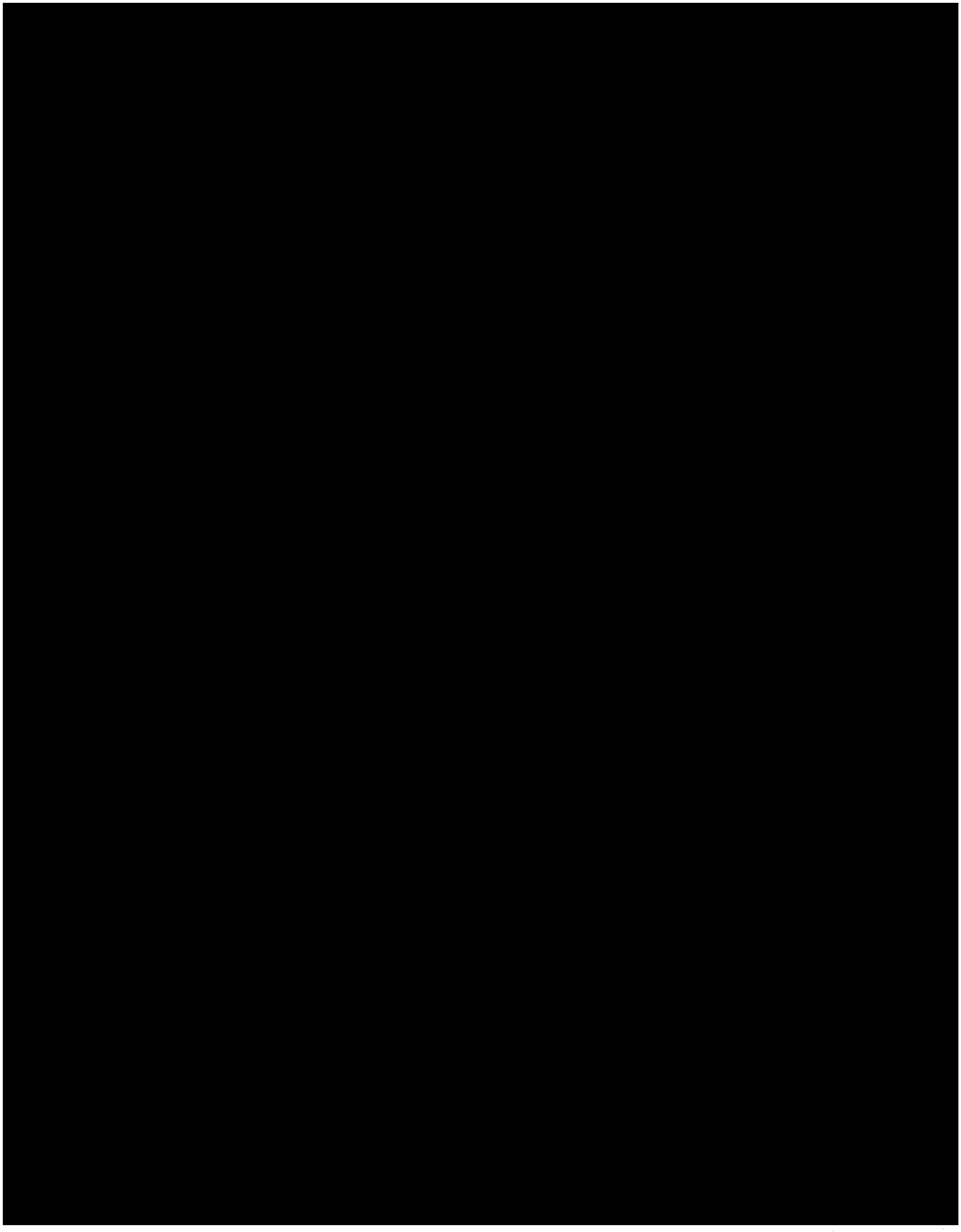
Drug Substance

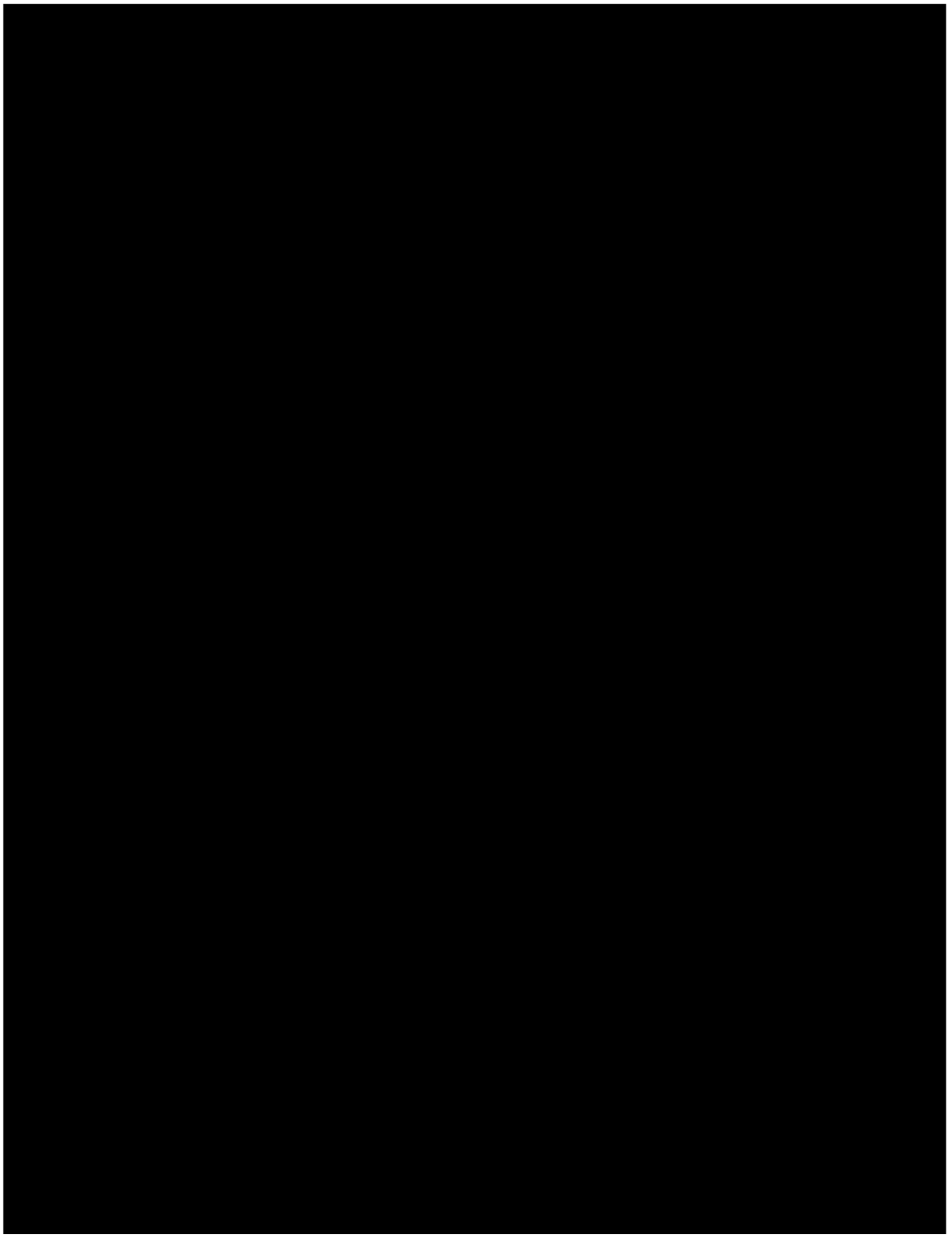
Peginterferon alfa-2b Drug Substance is synthesized, purified, tested and stored at: Schering-Plough (Brinny) Co., Innishannon, Co. Cork, Ireland. license 0994, [redacted]

Schering-Plough (Brinny) is responsible for the synthesis, purification and release of the Bulk drug Substance. Schering-Plough (Brinny) Co. is also responsible for the fermentation, purification and release of the [redacted] Interferon Alfa-2b Drug Substance used as a starting material in the Peginterferon Alfa-2b Drug Substance

Summary of Synthesis and Purification Process for Peginterferon Alfa-2b Drug Substance

Peginterferon alfa-2b Drug Substance (peginterferon alfa-2b) is prepared by reacting [redacted] Interferon Alfa-2b Drug Substance (IFN) in solution with monomethoxypoly(ethylene glycol) [redacted] MW 12000 [redacted] PEG 1200). The reaction involves the formation of a "urethane" bond between the PEG and amino groups [redacted]





[redacted]

Drug Product

PEG-Intron Powder for Injection Sterile Manufacturing Areas:

PEG-Intron Powder for Injection is manufactured in [redacted] Raw materials and packaging components required for the PEG-Intron Powder for Injection

manufacturing process are stored in the [redacted] or in [redacted] of the [redacted]

Drug Substance in [redacted] required for production in [redacted] is stored in the freezer located in the [redacted] Drug Substance in [redacted] is also stored on an interim basis in a [redacted] located in [redacted] Building 4.

Compounding:

[redacted]

Filling:

Product vial filling takes place under class [redacted] conditions on the filling line located in [redacted] as follows: [redacted]

Lyophilization:

The PEG-Intron Powder for Injection product vials are lyophilized in [redacted] using the following cycle:

[redacted]

[redacted]

Capping:

[redacted] to the vial capper located in [redacted] for capping, sealing and crimping. Seal quality checks are performed. Capped product vials are fed via conveyors from the vial capper into [redacted] machines located in the Packaging Hall [redacted] Alternatively, capped product vials can be packed into trays in the Packaging [redacted] for transfer to [redacted] where they are inspected in Inspection and Capping [redacted]

Inspection and Packaging:

Capped product vials are inspected [redacted] in the Packaging Hall [redacted] or in Inspection and Capping [redacted]